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Letter to the Editor

Cross-neutralization of Omicron subvariants after heterologous NVX-CoV2373 boosters: Comparison between prior SARS-CoV-2-infected and infection-naive individuals

Dear editors

Since the first emergence in November 2021, the SARS-CoV-2 B.1.1.529 (Omicron) variant had become the dominant strain worldwide, leading to a large increase in the number of COVID-19 cases. After then, the antecedent Omicron BA.1 strain has been replaced by Omicron BA.4 and BA.5 subvariants, which are highly transmissible, and more immune-evading from vaccines (1). In a previous study by Yadav et al., reduced neutralization was observed against Omicron variant after 2-dose primary series vaccination (2). Booster vaccination is expected to enhance the cross-neutralization activity against Omicron subvariants.

The Nuvaxovid™ (NVX-CoV2373), a recombinant protein-based vaccine with feasible cold chain requirement, has been granted as a booster in several countries. Although NVX-CoV2373 booster vaccination presented promising immunogenicity, its cross-reactive immunogenicity against Omicron subvariants of SARS-CoV-2 has not been reported (3,4). From March to April of 2022, we prospectively recruited individuals scheduled to receive NVX-CoV2373, including those who had completed two-dose (n = 9, aged 19–49 years) or three-dose (n = 41, aged ≥60 years) vaccination approximately five months ago (Supplementary Fig. 1). They previously received either homologous or heterologous vaccination with ChAdOx1, BNT162b2, or mRNA-1273 (Supplementary Table 1). Anti-nuclear capsid protein (anti-N) antibodies were measured in these individuals to determine prior SARS-CoV-2 infection status using the SARS-CoV-2 IgG assay (Abbott Laboratories, Chicago, IL, USA). This study was approved by the Institutional Review Boards of Korea University Guro Hospital (2021GR0099) and International St. Mary's Hospital (S21MIME0045). Written informed consent was obtained from all participants.

Baseline characteristics of the participants are presented in Supplementary Table 1. Participants in the third-dose booster group completed two-dose primary series vaccination 5.5 months (median) ago, while those in the fourth-dose booster group received the prior third dose 4.7 months (median) ago (Supplementary Fig. 1). Individuals with fourth-dose booster were older than those with third-dose booster, since the fourth-dose booster had been recommended only for the older-adults during the study period. Thus, the median age of individuals with the third and fourth dose were 27 (range, 19–68 years) and 65 (range, 60–70) years, respectively.

Neutralizing antibody (nAb) titers against Wuhan-1 strain and Omicron subvariants BA.1 and BA.5 were assessed in age/sex-matched, prior-infected (n = 9) and uninfected individuals (n = 9), before (T0) and three weeks (T1) after the fourth dose of vaccination. These values were compared with the titers of infection-naive individuals who received the third dose (n = 6). For the nAb analysis, a plaque reduction neutralization test (PRNT) was performed using wild-type SARS-CoV-2 (βCoV/Korea/KCDC03/2020 NCCP No. 43,326), Omicron BA.1 subvariant (GRA: B.1.1.529 NCCP No. 43,408), and Omicron BA.5 subvariant (GRA: BA.5 NCCP No. 43,426) as described previously (5). The methods of PRNT and statistical analysis were described in Supplementary appendix. Among infection-naive individuals, although fold-change was smaller after the fourth dose, third (3.8–14.7-fold) and fourth doses (1.8–2.5-fold) boosted the nAbs against both wild-type and Omicron subvariants (Fig. 1A). However, only a marginal increase (1.0–1.4-fold) in nAb titers was observed in prior-infected individuals after the fourth dose (Fig. 1A).

Median nAb titers for Omicron BA.5 were 212 in infection-naive, third-dose recipients; 127 in infection-naive, fourth-dose recipients; and 679 in prior-infected, fourth-dose recipients (Fig. 1B). Prior-infection was associated with significant cross-reactive immunity against Omicron BA.5. Therefore, booster vaccination would be more helpful in infection-naive individuals. Before booster vaccination, the nAb titers against BA.1 or BA. 5 variants were lower compared to those against the wild-type strain by a factor of 4 to 22. The fold difference between wild-type strain and Omicron subvariants became smaller in infection-naive individuals after booster vaccination (Supplementary Table 2 and Supplementary Fig. 2).

Additionally, we investigated the antibody kinetics up to 3 months among individuals ≥60 years who received NVX-CoV2373 as fourth-dose booster (n = 41), stratified by prior SARS-CoV-2 infection. Anti-SARS-CoV-2 spike protein (anti-S) IgG antibodies were measured before booster (T0), three weeks (T1), and three months (T2) after booster dose (Supplementary Fig. 1) using electrochemiluminescence immunoassay (Elecsys anti-SARS-CoV-2 spike ECLIA, Roche Diagnostics, Pleasanton, CA, USA), according to the manufacturer's instructions. Eighteen (43.9%) participants tested positive for anti-N antibody at baseline screening, and one participant became positive-converted during the follow-up period. Anti-S antibody titers were higher in prior-infected individuals than in infection-naive ones (Fig. 2). Fourth-dose vaccination did not increase the anti-S antibody titers in prior-infected individuals, demonstrating ceiling effect.

In conclusion, both third- and fourth-dose heterologous NVX-CoV2373 boosters enhanced cross-reactive immunity against Omicron BA.1/BA.5 subvariants among infection-naive individuals. Although repeated vaccination at short intervals showed ceiling effect in prior-infected individuals, which was consistent with previous reports, prior SARS-CoV-2 infection may provide better cross-protection against diverse Omicron subvariants (6,7).

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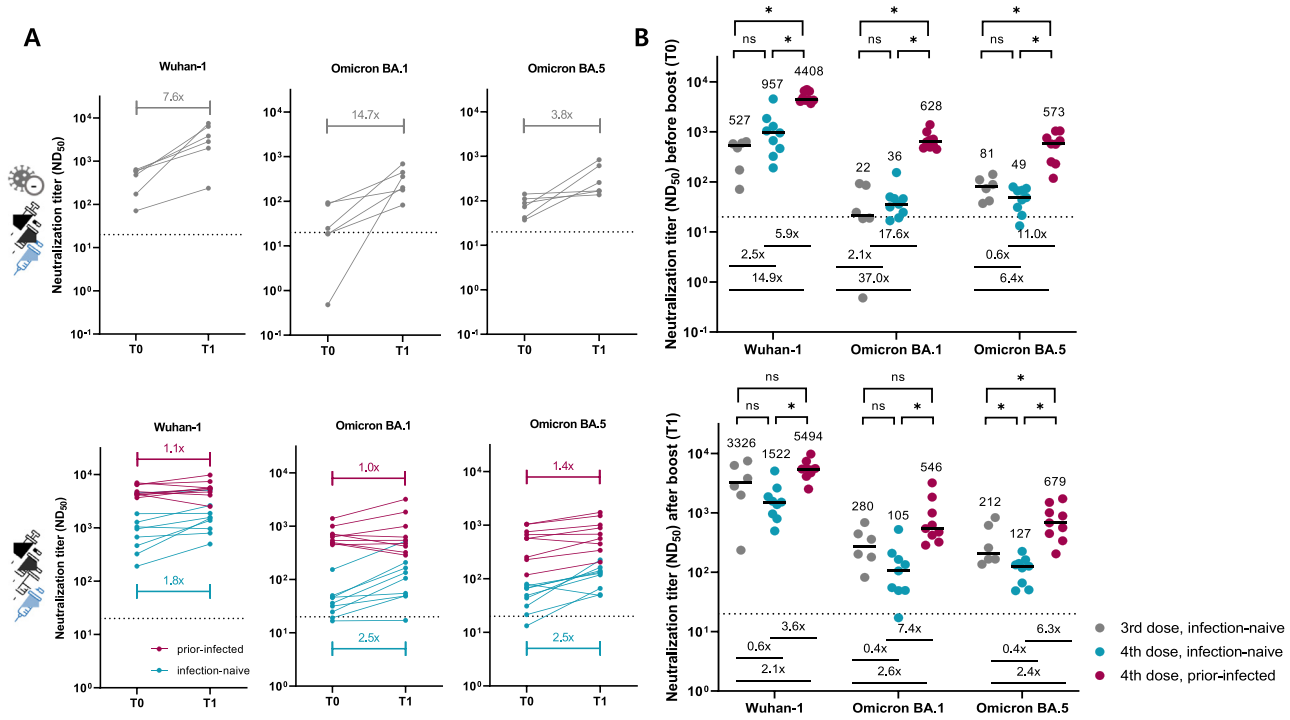

Fig. 1. Neutralization titers against wild-type Wuhan-1 strain and Omicron subvariants BA.1 and BA.5 in individuals who received the third or fourth dose vaccination with NVX-CoV2373. In panel A, upper part shows neutralization titers against wild-type Wuhan-1 strain and Omicron subvariants BA.1 and BA.5 in six infection-naive individuals before (T0) and at three weeks (T1) after the third dose of vaccination with NVX-CoV2373 excluding three anti-N antibody-positive recipients. Lower part of panel A shows neutralization titers against wild-type Wuhan-1 strain and Omicron subvariants BA.1 and BA.5 in nine infection-naive and nine prior-infected individuals before (T0) and at three weeks (T1) after the fourth dose of vaccination with NVX-CoV2373. Fold-changes of geometric mean titers are presented in panel A. In Panel B, neutralizing antibody titers against wild-type Wuhan-1 strain and Omicron subvariants BA.1 and BA.5 are compared at each time point (T0 and T1) depending on prior infection and vaccine dose (third versus fourth). Median titers (horizontal black lines) are presented with the median titer values. The median neutralizing titer (ND50) was defined as the concentration of the antibodies that reduced the number of viruses by 50%.

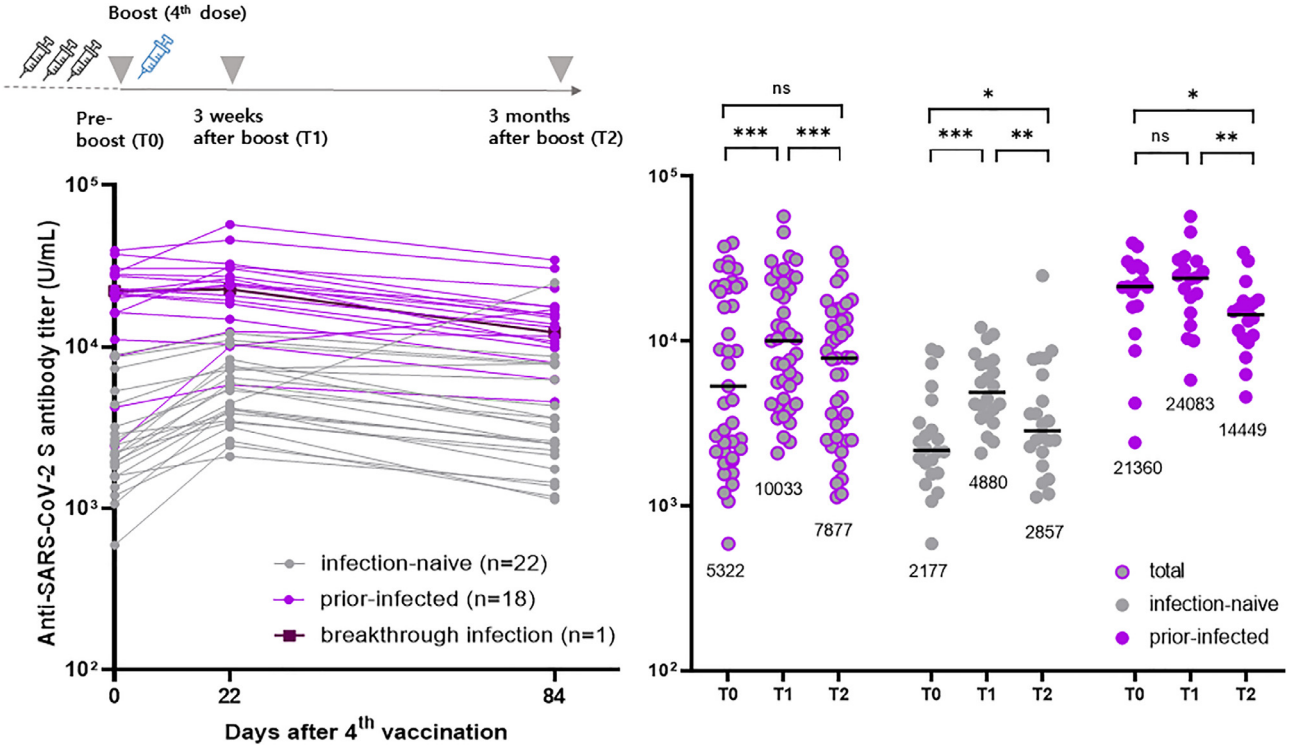

Fig. 2. Anti-SARS-CoV-2 spike protein (anti-S) IgG antibody kinetics, stratified by previous SARS-CoV-2 infection status. Anti-S antibody titers in samples obtained from 41 participants before fourth dose (T0) and 3 weeks (T1) and 3 months (T2) after the fourth dose. Median titers (black bars) are shown numerically. *P-value* resulting from Wilcoxon test ($^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$).

Declaration of Competing Interest

The authors declare no conflict of interest.

CRediT authorship contribution statement

Min Joo Choi: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Validation, Writing – original draft, Writing – review & editing. **Ju-Yeon Choi:** Data curation, Formal analysis, Methodology, Validation, Writing – review & editing. **Hakjun Hyun:** Investigation, Writing – review & editing. **Eliel Nham:** Investigation, Writing – review & editing. **Hye Seong:** Investigation, Writing – review & editing. **Jin Gu Yoon:** Investigation, Writing – review & editing. **Ji Yun Noh:** Investigation, Writing – review & editing. **Hee Jin Cheong:** Investigation, Writing – review & editing. **Woo Joo Kim:** Investigation, Writing – review & editing. **Su-Hwan Kim:** Methodology, Writing – review & editing. **Hyeonji Jeong:** Methodology, Writing – review & editing. **Min-Seong Kim:** Methodology, Writing – review & editing. **Byoungguk Kim:** Formal analysis, Methodology, Project administration, Validation, Writing – review & editing. **Joon Young Song:** Conceptualization, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Supervision, Validation, Writing – original draft, Writing – review & editing.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jinf.2022.09.018.

References

1. Prillaman M. Prior Omicron infection protects against BA. 4 and BA. 5 variants. *Nature* 2022.
2. Yadav PD, Sapkal GN, Sahay RR, Patil DY, Agrawal S, Adsul B, et al. Reduced neutralizing antibody response in naïve Covishield vaccinees against Omicron emphasizes booster vaccination. *J Infect* 2022.
3. Mallory RM, Formica N, Pfeiffer S, Wilkinson B, Marcheschi A, Albert G, et al. Safety and immunogenicity following a homologous booster dose of a SARS–CoV-2 recombinant spike protein vaccine (NVX-CoV2373): a secondary analysis of a randomised, placebo-controlled, phase 2 trial. *Lancet Inf Dis* 2022.
4. Munro AP, Janani L, Cornelius V, Aley PK, Babbage G, Baxter D, et al. Safety and immunogenicity of seven COVID-19 vaccines as a third dose (booster) following two doses of ChAdOx1 nCov-19 or BNT162b2 in the UK (COV–BOOST): a blinded, multicentre, randomised, controlled, phase 2 trial. *Lancet* 2021;**398**(10318):2258–76.
5. Noh JY, Kwak JE, Yang JS, Hwang SY, Yoon JG, Seong H, et al. Longitudinal assessment of antisevere acute respiratory syndrome coronavirus 2 immune responses for six months based on the clinical severity of coronavirus disease 2019. *J Infect Dis* 2021;**224**(5):754–63.
6. Munro AP, Feng S, Janani L, Cornelius V, Aley PK, Babbage G, et al. Safety, immunogenicity, and reactogenicity of BNT162b2 and mRNA-1273 COVID-19 vaccines given as fourth-dose boosters following two doses of ChAdOx1 nCoV-19 or BNT162b2 and a third dose of BNT162b2 (COV-BOOST): a multicentre, blinded, phase 2, randomised trial. *Lancet Inf Dis* 2022.
7. Noh JY, Cheong HJ, Kim WJ, Choi JY, Lee HW, Kim SS, et al. Robust neutralizing antibody responses after single-dose BNT162b2 vaccination at long intervals from prior SARS-CoV-2 infection and ceiling effect with repeated vaccination: running title: optimal vaccination interval and ceiling effect. *J Inf* 2022.

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